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Role of inflammatory markers in the preoperative evaluation of patients undergoing salvage total hip arthroplasty

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ABSTRACT

Surgeons may use laboratory tests, including erythrocyte sedimentation rate, C-reactive protein (CRP), and white blood cell count, as well as joint aspirations to diagnose prosthetic joint infections. There is a paucity of literature correlating preoperative inflammatory markers with risk of infection in the setting of salvage total hip arthroplasty (THA). This retrospective case analysis included patients who underwent a THA salvage procedure a minimum of 3 months after a failed fixation of a proximal femur or acetabulum, with a goal of assessing the utility of inflammatory markers as a screening tool in preoperative evaluation of salvage THA. Eighty-five patients met inclusion criteria. Thirteen patients were diagnosed with an infection preoperatively or intraoperatively during salvage THA. An elevated preoperative CRP level was a significant marker for infection. A CRP of 7.1 produced 80% sensitivity, 88% specificity, and a receiver operating characteristic curve of 0.840. There was a high rate of perioperative complications (17.6%) in salvage THA regardless of the presence of infection. In conclusion, CRP levels are useful in the preoperative evaluation for periprosthetic joint infection before salvage THA.

KEYWORDS diagnosis; infection; inflammatory markers; laboratory tests; salvage; total hip arthroplasty

Salvage total hip arthroplasty (THA) has been well described as an effective treatment, but complication rates remain high when compared to the initial THA.[1–8] Due to the devastating morbidity of a prosthetic joint infection (PJI), infection at the surgical site must be ruled out before implantation of a prosthesis.[9,10] Prior studies have defined the role of the inflammatory markers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in the diagnosis of periprosthetic joint infection. Literature supports the use of a combination of joint aspiration analysis and serum laboratory markers such as white blood cell count (WBC), ESR, and CRP to aid in the diagnosis of a joint infection.[11–15] The Musculoskeletal Infection Society has released criteria to determine the presence of periprosthetic joint infection based on multiple clinical and laboratory findings, including elevated inflammatory markers.[16] There is a paucity of literature that correlates preoperative elevated levels of inflammatory markers with risk of infection in the setting of a THA salvage procedure for a failed internally fixated hip fracture. The primary purpose of this study was to determine the degree of elevated inflammatory markers in patients with failed open reduction internal fixation (ORIF) of the acetabulum or proximal femur. The secondary purposes were to determine the sensitivity, specificity, predictive values, and receiver operating characteristics (ROC) of inflammatory markers, alone and in combination, in predicting culture-positive infection in patients with failed ORIF of the acetabulum or proximal femur.

METHODS

The study was approved by the institutional review board of Baylor Scott and White Medical Center – Temple. The electronic medical records were queried to identify all patients ≥18 years who had undergone surgical treatment with the CPT codes 27132 (conversion of previous hip surgery to THA) or 20680 (removal of hardware, deep) in combination with 27130 (THA) or 11981 (placement of

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antibiotic delivery device) between January 1, 2000, and December 31, 2014. Patients were selected for the study based on evidence of salvage THA or conversion to antibiotic spacer due to avascular necrosis, nonunion, posttraumatic arthritis, or infection, with failure occurring a minimum of 3 months after the index hip surgery. Exclusion criteria included known systemic inflammatory disease, known active infection or cancer, and follow-up <1 year.

Of the 399 patients identified, 85 met all inclusion and exclusion criteria. Demographic data, including age, sex, and body mass index, were collected. Known medical comorbidities were collected, with special attention to comorbidities such as diabetes mellitus, gout, renal disease, cardiovascular disease, osteoporosis, history of or current deep vein thrombosis/pulmonary embolism, and smoking status that may cause elevations of inflammatory markers.

Information regarding the index injury and treatment was recorded and included diagnosis, date and type of procedure, and perioperative complications. Information regarding the THA salvage procedure was recorded and included time to failure, failure diagnosis, and preoperative evaluation, including serum WBC, ESR, and CRP and preoperative hip aspiration.[14] The date of surgery, type of procedure, intraoperative cultures, use of preoperative antibiotics, and perioperative complications were noted. Preoperative infection was diagnosed by positive preoperative cultures, two or more positive intraoperative cultures, or the presence of gross purulence at the time of surgery or aspiration. The postoperative course was followed for at least 1 year for evidence of postoperative complications, including any further surgical interventions on the affected hip and the presence of new or chronic infection.

Characteristics of the data were summarized using frequencies and percentages for categorical variables. Means and standard deviations, or medians and ranges as appropriate, were provided for continuous variables. The independent sample *t*-test was used for bivariate comparisons of the normally distributed variables. The Wilcoxon-Mann-Whitney test was used for bivariate comparisons of the nonnormally distributed variables. The chi square test, or Fisher's exact test when appropriate, was used for bivariate comparisons of the categorical variables. A logistic regression analysis was performed with infection as the outcome. The model was evaluated based on the C-statistic. ROC curves were calculated for the unadjusted logistic model and used to find cutoff points, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. Significance was defined as $P < 0.05$.

RESULTS

There was no statistically significant difference between infected and noninfected patients in respect to age, body mass index, and demographic variables *(Table 1)*. Preoperative infection was diagnosed in 13 patients (15.3%) by either preoperative aspiration (4 patients) or positive intraoperative cultures (11 patients) during the THA salvage procedure. Postoperative PJI following salvage THA in the absence of positive pre- or intraoperative cultures was not considered a preoperative infection. The mean interval from the index internal fixation procedure to THA salvage procedure was 106.1 months (range 3.0–1247.3)—11.6 months for infected patients and 27.1 months for noninfected patients ($P = 0.24$).

Table 1. Demographic information and comorbidities for 85 patients undergoing salvage total hip arthroplasty

Variable	Not infected (n = 72)	Infected (n = 13)	*P* value
Gender			0.55
Male	27 (82%)	6 (18%)	
Female	45 (87%)	7 (13%)	
Smoker	37 (82%)	8 (18%)	0.81
Diabetes mellitus	12 (92%)	1 (8%)	1.00
Gout	5 (83%)	1 (17%)	0.58
Osteoporosis/osteopenia	1 (100%)	0	1.00
Renal disease	3 (100%)	0	0.42
Cardiovascular disease	44 (85%)	8 (15%)	0.79
Chronic infection	4 (100%)	0	0.52
Prior deep vein thrombosis or pulmonary embolism	9 (75%)	3 (25%)	0.10
Prior cancer	7 (87%)	1 (13%)	0.34

There was no statistically significant difference between the noninfected population and infected population comparing the failure diagnosis, type of index procedure, interval to THA salvage procedure, or type of first salvage procedure *(Table 2)*. No patients with failed closed reduction with percutaneous pinning were infected. The majority (69%) of patients in the infected group had ORIF as their index procedure (9 of 13 patients), and 18% of the ORIF group (9 of 49 patients) were infected. There was no statistically significant association between perioperative complications, primary index procedure type, or the type of first salvage procedure and infection in patients. Both infected and noninfected groups had a high rate of perioperative complications *(Table 3)*.

A total of 13 patients (13/85, 15.3%) were diagnosed with infection. Preoperatively, 20% (2 of 10 patients) had positive cultures and 22% (2 of 11 patients) had positive synovial analysis. There were 19 patients with intraoperative cultures drawn, and 58% (11 of 19 patients) were culture negative. However, 27% (3 of 11 patients) were culture negative intraoperatively but had preoperative cultures positive for infection. One patient had negative intraoperative cultures and developed an infection postoperatively. There

Table 2. Perioperative variables for 85 patients undergoing salvage total hip arthroplasty

Variable	Overall (n = 85)	Not infected (n = 72)	Infected (n = 13)
Initial diagnosis			
Trauma	69 (81%)	58 (84%)	11 (16%)
Other	16 (19%)	14 (16%)	2 (12.5%)
Failure diagnosis			
Posttraumatic arthritis	36 (42%)	31 (86.1%)	5 (13.9%)
Avascular necrosis	24 (28%)	22 (91.7%)	2 (8.3%)
Nonunion/malunion	17 (20%)	14 (82.4%)	3 (17.7%)
Failed hardware	5 (6%)	5 (100%)	0
Infection	3 (4%)	0	3 (100%)
Index procedure type*			
Closed reduction with percutaneous pinning	13 (15%)	13 (100%)	0
Open reduction internal fixation	49 (58%)	40 (81.6%)	9 (18.4%)
Acetabular fracture	18 (21%)	14 (77.8%)	4 (22.2%)
Proximal femur fracture	26 (31%)	23 (88.55)	3 (11.5%)
Both	4 (5%)	2 (50%)	2 (50%)
Intramedullary nail	16 (19%)	13 (81.3%)	3 (18.8%)
Other	7 (8%)	6 (85.7%)	1 (14.3%)
Number of interval surgeries			
0	72 (85%)	61 (85%%)	11 (15.3%)
1	10 (12%)	9 (90%%)	1 (10%)
2	2 (2%)	1 (50%)	1 (50%)
3	1 (1%)	1 (100%)	0
Type of first salvage procedure**			
Arthroplasty and removal of hardware	71 (84%)	62 (87%)	9 (13%)
Arthroplasty	9 (11%)	9 (100%)	0
Removal of hardware and antibiotic spacer	4 (5%)	1 (25%)	3 (75%)
Arthroplasty and internal fixation	1 (1%)	0	1 (100%)

*$P = 0.31$, Fisher's exact test.
**$P = 0.38$, Fisher's exact test.

Table 3. Perioperative complications in 85 patients undergoing salvage total hip arthroplasty

Complication	Overall (n = 85)	Not infected (n = 72)	Infected (n = 13)
Anemia requiring transfusion	3 (4%)	3 (4%)	0
UTI or *C. difficile* infection	2 (2%)	1 (1%)	1 (8%)
Respiratory issue	2 (2%)	1 (1%)	1 (8%)
Hematoma	2 (2%)	2 (3%)	0
Wound complication	2 (2%)	1 (1%)	1 (8%)
Dislocation	1 (1%)	0	1 (8%)
Trauma	1 (1%)	0	1 (8%)
Metallosis	1 (1%)	0	1 (8%)
Nerve injury	1 (1%)	1 (1%)	0
Total	15 (18%)	9 (13%)	6 (46%)

UTI indicates urinary tract infection.

was no statistically significant difference in serum ESR and WBC between infected and noninfected populations *(Table 4)*. There was a significant difference when comparing the CRP of the infected and noninfected groups (12 vs 3.2 mg/L; $P = 0.001$).

A logistic regression model was fit to the data with infection as the response and WBC count, ESR, and CRP as covariates. Using stepwise, forward, and backward model selection methods, only CRP was included in the model. The C-statistic (0.845) indicated that the model predicted better than chance (0.50). The regression diagnostics did not violate assumptions. Three potential cutoff points were detected at a CRP of 14.2, 9.4, and 7.1 mg/L *(Table 5)*.

DISCUSSION

In this preliminary study analyzing the preoperative workup prior to salvage THA, a preoperative elevated CRP was the only laboratory value associated with increased risk of infection, with a cutoff of 7.1 mg/L demonstrating good sensitivity and specificity.

There have been studies suggesting an altered biochemical environment of a joint in a trauma setting compared to arthroplasty.[17–21] Neumaier et al demonstrated that in the acute setting, CRP levels were statistically higher in patients with more invasive procedures for proximal femur fractures.[17] In the setting of uncomplicated THA, Aalto et al demonstrated that 1 year after THA, the ESR remained elevated; however, CRP levels normalized by 3 weeks after surgery.[18]

A wide range of literature has analyzed the criteria to diagnose periprosthetic infection in primary total joint arthroplasty.[11–15,22] Spangehl et al prospectively analyzed preoperative and intraoperative testing in a large cohort of patients with THA for the likelihood of infection. In their study, a CRP level > 10 mg/L had a sensitivity of 96%, specificity of 92%, and negative predictive value of 99%. They suggested that CRP $>$ 10 mg/L should encourage a hip aspiration and synovial culture of the affected joint.[15] Ghanem et al proposed that a CRP $>$ 10 mg/L and an ESR > 30 mm/h independently are highly suggestive (>90% sensitivity) of a periprosthetic infection, with the combination of both cutoffs greatly increasing the sensitivity of infection to 97.6%.[12]

One of the 13 patients in this study had negative intraoperative cultures but preoperatively had positive cultures for

Table 4. Laboratory infection workup in 85 patients undergoing salvage total hip arthroplasty

Preoperative bloodwork	Overall: median (SD)	Not infected: median (range)	Infected: median (range)	*P* value
White blood cells ($\times 10^9$/L)	7.3 (2.2)	7.2 (2.3–15.7)	7.3 (5.6–9.6)	0.824
Erythrocyte sedimentation rate (mm/h)	15.0 (18.9)	14 (3.0–67.0)	16.5 (6.0–100)	0.067
C-reactive protein (mg/L)	4.4 (8.0)	3.2 (2.0–22.0)	12.0 (2.9–41.5)	0.001

Table 5. Logistic regression model fit to the data with C-reactive protein levels and infection (preoperative and intraoperative)

Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)	ROC (95% CI)
14.2	40% (12.2–73.8)	96% (88.8–99.2)	57% (18.4–90.1)	92% (84.0–97.1)	89% (80.9–95.0)	0.680
9.4	70% (34.8–93.3)	95% (86.9–98.5)	63% (30.8–89.1)	96% (95.2–99.0)	92% (83.8–96.6)	0.823
7.1	80% (44.4–97.5)	88% (78.44–94.4)	47% (22.3–72.2)	97% (89.8–99.6)	87% (78.1–93.4)	0.840

CI indicates confidence interval; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristics.

infection. One patient preoperatively had a dry tap and only the gram stain could be performed by the lab. This reinforces the need for a multimodal approach to preoperative diagnosis of infection in this patient population.

There was a high rate of complications following the THA salvage procedure in the entire study population. There was no statistical difference in the perioperative complication rate between our infected and not infected cohorts. Studies comparing primary THA for femoral neck fractures and THA salvage procedures for failed internal fixation for femoral neck fractures have reported statistically significant higher overall complication rates in the THA salvage procedure and increased blood loss.[5–8] In the current study, anemia requiring transfusion was the most common complication as well.

The major limitation of this study was the small sample size, leaving the study underpowered to determine small differences between the infected and noninfected cohorts. There were multiple surgeons over an extended period, and therefore there were multiple preoperative protocols and intraoperative management in our study population. As intraoperative assessment of infection with biopsy, frozen section, or intraoperative cultures was inconsistent in this cohort, further studies to confirm the sensitivity of CRP as a screening tool in indolent infection are needed prior to wide adoption.

In conclusion, few reports are available to direct the preoperative workup of patients prior to salvage THA. Results from the current study demonstrate that CRP may be a fair screening tool for infection in these patients. The use of a CRP cutoff of >7 mg/L can be used in the setting of screening for risk of periprosthetic infection in salvage THA.

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